VIEWPOINT

Why we need a mouse version of a diagnostic test for autism

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21 MARCH 2018

If only we had a blood test for autism: A biological marker could help us detect autism early, avoiding the need to wait until language, social and cognitive issues become established. It would also enable us to develop treatments that alleviate difficulties and increase quality of life for people on the spectrum.

But so far, reliable **biomarkers** remain elusive, and we are stuck with behavioral markers for diagnosis.

Because of their genetic similarity to people, and their social behavior, mouse models hold potential for learning about the biology of autism. But designing mouse models that mirror the

complexity of autism has proven to be challenging.

We have learned much from developing autism measures for people about how to reliably and accurately assess the behaviors most important to an autism diagnosis. A mouse ‘diagnostic test’ could similarly bring consistency to studies using mouse models of autism.

It wasn’t easy to develop a standard and reliable measure of autism. In the 1980s, there was little consensus or consistency about how clinicians should evaluate autism and how to assess and prioritize its features in arriving at a diagnosis. Research findings were thus difficult to replicate.

In 1989, a group of researchers developed the Autism Diagnostic Observation Schedule (ADOS) to provide a standardized method for observing social communication and restricted, **repetitive behaviors** in people with autism[1]. The ADOS is now considered one of the gold-standard tests for diagnosing autism and related conditions.

The measure can be used across ages and language levels and is designed to address complexities such as changes in autism features with age and overlap with related conditions.

It works by creating a social context that is standardized; we look at a specific set of autism features and follow guidelines for quantifying them, and so clinicians at different sites can apply the test in a consistent manner. Yet it is flexible enough to adjust to the participant’s behaviors.

Mouse measures:

Because the ADOS has been central to research in autism, a ‘mouse ADOS’ to aid translation across species is an attractive idea. Are there ways to replicate the strengths of the ADOS in the mouse?

A major strength of the ADOS is its standardization. Researchers working with mouse models of autism have recognized the need for similarly replicable measures of mouse behavior. The ADOS includes approaches for measuring social reciprocity, for evaluating reasons for social difficulties and for providing standardized ‘presses,’ or prompts designed to see how different people respond to the same kind of social cue. Are these features present in mouse behavioral tests?

Researchers generally measure repetitive behaviors in mice — say, repetitive grooming — as they occur spontaneously, rather than in response to a press as in the ADOS. This approach may explain the large variability among labs in reports of repetitive behavior from the same mouse model.

The other feature mouse researchers often study is social behavior, often using the three-chambered task, in which a mouse is given a choice between an empty cage or one containing another mouse. This task works well for measuring one type of social behavior, but it doesn't reveal

much about social motivation or social reciprocity. Something like a mouse ADOS could address this need.

Taking turns:

By far the most interesting feature of the ADOS is the array of standardized presses, which are designed to elicit a type of behavior from a person with autism to but allow the person to respond in her own unique manner.

The tasks have an element of reciprocity: The examiner judges not just how a participant initiates social interactions, but also how she responds to overtures and builds reciprocal interactions. A challenge for mouse research is that the social-partner mice used in the tests may not behave consistently and cannot provide predictable presses for social reciprocity.

One promising way to circumvent this problem is to use tasks that have freely moving mouse social partners engage in self-selected social behaviors, and then examine the ability of the autism model mice to respond with social reciprocity. However, researchers do not always agree on the interpretation of behavior between mouse pairs, making this easier said than done.

Another strength of the ADOS in evaluating social behavior is the ability to rule out reasons for social difficulties that aren't central to autism — such as anxiety, aggression or hyperactivity.

In the case of mice, researchers often run control tasks to ensure that the animals can move and smell normally, as smell is important in the social world of mice. But these measures don't control for other confounds, such as social anxiety or aggression. Incorporating control tasks to address these alternative explanations would get us closer to a 'mouse ADOS.'

One approach that has gained traction is to test animals using explicit prompts, similar to the ADOS presses, for nonsocial behaviors. For example, can a hungry mouse respond in the most appropriate way to a prompt to get food?

Scientists use these 'operant' tasks to measure the ability to perform a specific behavior in response to a prompt to get a small food reward. For example, one operant task might be learning to touch an image on a screen because it is associated with a reward, and not spend time touching other possible objects on the screen.

Several mouse models of autism are impaired in this kind of operant task, even when their social interaction in the three-chambered task appears normal[2]. These findings mimic problems people with autism have in learning to choose the more rewarding image in a similar task[3].

We are using these kinds of operant tasks to measure decision-making in autism mouse models. This approach provides the mice opportunities to solve the task in their own way, but also provides

a standard environment for the animals to interact with, mimicking the standardized presses in the ADOS.

An exciting possibility is to develop tasks that integrate operant behavioral prompts for evaluating repetitive behaviors and social reciprocity in mouse models. This would more closely model what the ADOS measures in people on the spectrum.

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